Paroxysmal Nocturnal Hemoglobinuria

A Report of Two Cases

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH), also known as Marchiafava-Micheli's disease, is not a common disease. (Crosby,[1] in an excellent review, noted only 162 case reports published up to July 1953). It is, however, a disease of great general biologic interest, since it represents a unique kind of intravascular blood destruction apparently not limited to red blood corpuscles, since an abnormality of renal function seems to be a prerequisite, and since all known factors responsible for precipitated hemolysis—toxic, infectious, immunologic, genetic—can be excluded from etiologic consideration.

It is the purpose of this communication to emphasize a practical side of interest. Paroxysmal nocturnal hemoglobinuria may readily be confused with spherocytic hemolytic icterus and, hence, treated by splenectomy which is useless and even risky in this condition. This is illustrated by the first of the two cases herein reported. The second case demonstrates the seemingly paradoxical but well known phenomenon of a combination of phlebothrombosis with increased hemolysis and the beneficial effect of dicoumarin treatment.

The term nocturnal hemoglobinuria is not quite correct because hemosiderinuria rather than hemoglobinuria is a constant feature of the disease, and sleep rather than night is the essential inciting factor. The retention of carbon dioxide in the blood due to diminished pulmonary ventilation during sleep causes the increased hemolysis. The erythrocytes are at fault and susceptible to the proteolytic effect of normal plasma enzymes, especially if the acidity of the plasma rises during sleep. Erythrocytes of patients with this acquired disease are rapidly destroyed if transfused to normal persons, whereas normal erythrocytes transfused into patients with this disease survive a normal length of time.

The abnormal hemolysis in PNH takes place within the circulating blood, as contrasted with the accelerated destruction of the red corpuscles by the reticulo-endothelial system in other types of hemolytic anemia; hence, the relatively mild elevation of serum bilirubin and fecal and urinary urobilinogen, and the chief elimination of the liberated hemoglobin through the kidneys. Some of the iron derived from hemoglobin is lodged as hemosiderin in the renal epithelia and excreted in the urine where it can readily be identified by its Prussian-blue reaction in the sediment. Whereas the threshold for renal excretion of free plasma hemoglobin in normal persons has been found to be about 130 mg. per 100 ml. of plasma, the threshold may be as low as 50 mg. per 100 ml. in cases of this disease. Hence, the abnormality encountered in paroxysmal nocturnal hemoglobinuria involves the renal tubules also.

The susceptibility of the erythrocytes of patients with PNH to be destroyed by the proteolytic enzymes of normal plasma is not due to an abnormality of hemoglobin[3] but probably to a defect of the stromal protein.[1] The similar susceptibility of leukocytes and platelets in PNH suggests a similar defect of these cells.[1]

CASE REPORTS

CASE 1. A 38-year-old Caucasian man, a bartender, was admitted to the Los Angeles County Hospital on May 5, 1953, because of complaint of bloody appearing urine of three days' duration. The patient had noticed weakness and fatigability since the age of 20 but did not seek medical aid until 1941 when, because of anemia and jaundice, he was hospitalized in another city. A diagnosis of congenital hemolytic icterus was made and splenectomy was done. A report on this episode, obtained from the records of the hospital, contained no conclusive evidence of the diagnosis. It included notations, however, that the icterus index was increased to 37-52 units, that the blood was hemolyzed and that cholecystography showed a normally functioning gallbladder. Congestion and an increased amount of hemosiderin deposit were noted in the removed spleen. Since the operation the patient had led an active life, having served in the merchant marine during the war. He was a heavy drinker. On two occasions, in different hospitals, he received a blood transfusion for anemia. Except for this he was doing well until December 1952, at which time emergency operation was done for a perforated ulcer. After recovering the patient again was asymptomatic until three days before the present admission when, fol-

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Submitted August 31, 1954.

lowing an attack of low back pain, he noticed what he took to be blood in the urine. The color persisted until the time of entry to the hospital but did not cause dysuria.

The patient was well nourished and well developed. Slight icterus of the skin and of the sclerae was noted. The blood pressure was 110/70 mm. of mercury. The temperature, pulse and respiration rate were normal. The heart was not enlarged and the lungs were clear. The abdomen was normal except for the scars of two previous surgical procedures.

The urine was coffee-colored with 2 plus reaction for protein. Granular casts were seen, but no red cells. There was a strongly positive reaction for hemoglobin. The hemoglobin content of the blood was 8.8 gm. per 100 cc. Erythrocytes numbered 2,400,000 per cu. mm., with 30 per cent of the cells reticulocytes and thrombocytes in normal number. Leukocytes numbered 9,500 per cu. mm., with segmented neutrophils 66 per cent, lymphocytes 25 per cent, monocytes 7 per cent, eosinophils 1 per cent and basophils 1 per cent. In addition, there was anisocytosis, leptocytosis and polychromasia and Howell-Jolly bodies were noted. Result of a serologic test was negative for syphilis. Direct and indirect Coomb's tests were negative for antibodies. The icteric index was 33 units, the erythrocyte fragility normal, and the bone marrow hyperplastic, showing chiefly erythroid hyperplasia. The patient had been instructed to save a sample of urine each time he voided, and it was noticed that the morning specimens were much darker in color than the afternoon specimens. The dark, morning specimens contained hemoglobin, the light amber afternoon specimens did not. The result of Ham's acid hemolysis test for paroxysmal nocturnal hemoglobinuria was positive on several occasions. The urine was also strongly positive for hemosiderin. It gave a negative reaction for urobilinogen in a dilution of 1:10. The stool, however, contained a moderately increased amount of urobilinogen—490 mg. average per 24 hours.

A transfusion of two units of washed erythrocytes was given and, following this, the patient went into remission. He was discharged with hemoglobin content 10 gm. per 100 cc. of blood, erythrocytes 3,300,000 per cu. mm. and leukocytes 10,100 per cu. mm., and remained well at least during the next monthly clinic visits.

As was pointed out previously, the renal threshold for excretion of free plasma hemoglobin is lowered in PNH. There was no evidence in the foregoing case of any other impairment of renal function. Because aminoaciduria is known to be a fine indicator of impaired tubular reabsorptive capacity in some cases, it was looked for in this case but was not found. White blood corpuscle and platelets were not affected by the disease.

Although there are a few cases on record of PNH in which the osmotic fragility of the red corpuscles was increased or spherocytosis was present, indicating a combination of spherocytic hemolytic jaundice with PNH,[1] no such findings could justify this diagnosis in the foregoing case. It is probable, therefore, that the patient had PNH from the onset and at the time splenectomy was carried out. It is important to realize that hemoglobinuria may be absent in the initial stage of the disease when only increased hemolysis and hemoglobinemia are found.

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CASE 2. A 50-year-old Caucasian man was admitted to the Veterans Administration Hospital in Long Beach on January 27, 1953, because of pain and swelling of the left leg for approximately a month. The patient told of having intermittent episodes, over the previous five years, of dark urine in the morning. The condition lasted one to three days. There was also history of anemia, for which iron and vitamin B_{12} had been prescribed.

Upon physical examination the patient was noted to be pale and the sclerae slightly icteric. The blood pressure was 120/60 mm. of mercury, the pulse 80 and the temperature 100° F. The heart, lungs and abdomen were normal. A moderate edema of the legs was noted and there was slightly increased warmth, but no redness; tenderness was noted in the calf behind the knee and on the inner aspect of the thigh up to the groin on the left, and slight tenderness in the right calf.

There was hemoglobin in the urine. The number of leukocytes in the blood, determined daily, varied from 4,250 to 1,860 per cu. mm. Erythrocytes varied from 1,860,000 to 3,510,000 per cu. mm., with the proportion of reticulocytes ranging from 3.7 per cent to 10.5 per cent. Hemoglobin content varied between 7.7 gm. and 11.3 gm. per 100 cc.—the higher level having been reached after transfusion of 1,000 cc. of washed erythrocytes. A Donath-Landsteiner cold agglutinin test was negative. Bone marrow aspirate showed erythroid hyperplasia. Erythrocyte fragility was normal, and a Coomb's test negative for antibodies. There was negative reaction to a test for syphilis. The result of an acid hemolysis test for PNH was positive. Because thrombophlebitis was becoming more severe, the surgical staff advised and performed a ligation of the inferior vena cava. The patient then was given dicoumarin and improvement was noted from that point on. He was later discharged for outpatient care with a prescription of maintenance dosage of dicoumarin. Of interest to note is that the hemoglobin content, which was increased to 11.3 gm. per 100 cc. after the transfusion of washed red cells, remained at that level following the administration of dicoumarin.

Case 2 is remarkable for the combination of phlebothrombosis and beneficial effect of dicoumarin therapy in PNH. Almost 50 per cent of patients with PNH die of thromboses, chiefly abdominal or cerebral. Whether the thrombotic tendency is due to an abnormality of the readily agglutinating platelets[1] or to localized accumulation of erythrocyte stromas[3] is not certain. It is likewise uncertain whether the abdominal pain, headache or pain in the back or shoulder is due to small vascular thromboses[1] or to porphyria.[3]

The persistent leukopenia in Case 2 substantiates Crosby's opinion that leukocytes as well as erythrocytes are susceptible to premature destruction by proteolytic enzymes of normal plasma. As to the blood platelets, no morphologic abnormality was noted in the patient. There was no indication that crises of temporary bone marrow failure, with resulting increased anemia, leukopenia or pancytopenia, might have occurred in either of the two cases here reported. Such crises, however, are common in various types of genetically determined hemolytic diseases.

It stands to reason that treatment with cortisone or corticotropin (ACTH) and splenectomy in cases of PNH have no rational basis. Furthermore, it is important to know that whole blood transfusions may aggravate rather than improve the hemolysis by introduction of the donor's normal plasma which may be a hemolyzing factor for the patient's red corpuscles. Only carefully washed normal red cells deprived of admixture of plasma should be transfused.

For the exact diagnosis of this disease, two simple laboratory tests in addition to Ham's acid hemolysis test are available and should be used, particularly if no hemoglobinuria was observed at the time of examination: (1) Test for hemosiderinuria by adding ferric chloride to the urinary sediment; (2) Hegglin's diminished heat resistance test consisting of hemolysis if the blood of the patient is kept at a temperature of 37 degree C. for 6 to 24 hours.

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Healed Dissecting Aneurysm of the Aorta

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ACCURATE DIAGNOSIS of acute dissecting aneurysm of the aorta has become commonplace, owing to increased awareness of the variable clinical syndrome. A continuing challenge is the recognition of so-called healed dissecting aneurysm, which, because of the presence of aortic systolic and/or diastolic murmurs, may mimic syphilitic aortic aneurysm or chronic rheumatic heart disease. Healing occurs in 13 to 27 per cent of all instances of dissecting aneurysms[2, 10] and results from reentry of the false channel into the aortic lumen at some point distal to the site of initial intimal rupture. There is thus no further extension, and patients may survive for long periods without symptoms, ultimately dying of congestive heart failure, rupture of the aorta or cerebral hemorrhage.

CASE REPORT

The following case illustrates the characteristic history and cardinal signs of healed dissection of the thoracic aorta.

A 60-year-old white man was admitted to hospital in May, 1954, because of recurrent paroxysmal nocturnal dyspnea of five months' duration. The illness had begun in September, 1949, with sudden, excruciating mid-back pain which radiated straight through to the epigastrium and lower sternal area. The patient said he felt extremely weak at that time but he remembered no sweating, dizziness, headache, cough, dyspnea or weakness of limbs. There were no gastrointestinal or genitourinary complaints. Medication (type not known) gave no relief from the persistent pain, which spead upward to the interscapular area and both shoulders and then slowly subsided in 13 days. The patient was not hospitalized, and no data are available regarding the cardiovascular status at that time. After that episode he was asymptomatic, except for a lifelong tendency to frequent respiratory infections, until January, 1954, when paroxysmal nocturnal dyspnea developed. The attacks occurred weekly, lasted 20 minutes to an hour and were associated with wheezing, productive cough and a sense of epigastric fullness. The patient said he had not had exertional dyspnea, angina or edema at the ankles. The nocturnal episodes became more frequent and severe, and the patient was hospitalized following a prolonged attack.

The family history was unknown to the patient. Past history was negative except for chronic bronchitis, diagnosed in 1924, and a tendency toward frequent "chest colds." Right mastoidectomy had been performed in 1934. Syphilis was denied by name and manifestations, as was antisyphilitic therapy.

Physical examination. The temperature was 98.4° F. (oral); pulse, 120, regular; respirations, 24 per minute; blood pressure, 230/110 mm. of mercury and 210/106 mm., right and left arm, respectively. The patient was slightly dyspneic and orthopneic, but not acutely ill. The neck and superficial forehead veins were distended. A mastoidectomy scar on the right, bilateral arcus senilis, retinal arteriolo-

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Submitted September 16, 1954.